

Comparison of Intravenous Magnesium Sulphate Combined with Acetaminophen Versus Intravenous Nalbuphine in Chronic Obstructive Pulmonary Disease Patients Undergoing Elective Cholecystectomy

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ABSTRACT

Objective: To compare the analgesic efficacy of non-opioid anesthesia (NOA) using intravenous Magnesium Sulphate combined with intravenous Acetaminophen versus intravenous Nalbuphine in COPD (chronic obstructive pulmonary disease) patients undergoing elective laparoscopic cholecystectomy.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Anesthesia, Combined Military Hospital, Rawalpindi Pakistan, from Aug 2023 to Feb 2024.

Methodology: Primary variables measured were per-operative mean heart rate, mean arterial pressure, time to rescue analgesia and median pain scores at 1-, 3- and 6-hour intervals. Secondary variables were the incidence of hypotension, respiratory depression, nausea and vomiting between both groups.

Results: When observing the primary variables, mean time to first dose of rescue analgesia required was 122.49 ± 14.01 minutes in Group-M versus 151.71 ± 10.36 minutes in Group-N ($p < 0.001$). When comparing the post-operative median pain scores, median pain score at 1 hour post-operatively was 3.00 (IQR=1.00) in Group-M versus 2.00 (IQR=1.00) in Group-N ($p = 0.353$). Scores observed 3 hours post-operatively were 3.00 (IQR=0.00) versus 3.00 (IQR=0.00) between Group-M and Group-N ($p = 0.626$). Finally, median pain scores 6 hours post-operatively showed 3.00 (IQR=0.00) versus 3.00 (IQR=0.00) between both groups respectively ($p = 0.154$).

Conclusion: We conclude that intravenous Magnesium Sulphate with Acetaminophen is a good alternative and provides superior adverse effect profile than Nalbuphine in patients with COPD.

Keywords: Acetaminophen, Cholecystectomy, COPD, Magnesium Sulphate, Nalbuphine.

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INTRODUCTION

Chronic obstructive pulmonary disease encompasses irreversible loss of respiratory tract elasticity resulting in parenchymal destruction of air spaces unable to provide an interface for oxygen uptake.¹ It is the third leading cause of death worldwide with an estimated 3.23 million deaths in 2019.² Patients with COPD are in the later age group of life between 55-75 years of age and with associated co-morbidities such as chronic smoking, diabetes, hypertension, and ischemic heart disease.³ The optimization of the disease before surgery and associated co-morbidities are a challenge to the anesthetist especially due to profound respiratory compromise.⁴ Even though regional techniques have been developed to avoid giving general anesthesia in these patients where possible, co-morbidities and refusal by patients to opt for regional and neuraxial

techniques warrant attention to the choice of drugs to be given to these patients.⁵

Intravenous opioids have been used as first line agents for pain relief in majority of surgeries. However, with the advent of newer drugs and techniques providing effective analgesia, their use in curtailed in patients susceptible to respiratory depression and airway compromise.⁶ Patients with COPD are at an added risk for these complications and better alternatives need to be investigated for their analgesic efficacy for better patient comfort while preventing complications. This associated with the additional complications of pneumoperitoneum in laparoscopic surgeries makes a strong argument for the need of special care in the drugs being given under general anesthesia.⁷

The concept of opioid free anesthesia (OFA) has gained wide acceptance in majority of health care setups.⁸ Various drugs are being used, the most important being Magnesium Sulphate, Ketamine, Lignocaine and Dexmedetomidine among others.

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Studies have proved their ability to provide effective analgesia as well. The use of these drugs can be beneficial in patients where the use of opioids is deleterious and associated with increased complications.

Our study aims to compare the analgesic efficacy of non-opioid analgesia by using intravenous Magnesium Sulphate combined with intravenous Acetaminophen versus intravenous Nalbuphine in patients undergoing elective cholecystectomy.

METHODOLOGY

This quasi-experimental study was carried out at the Department of Anesthesiology, Combined Military Hospital Rawalpindi, Pakistan from Aug 2023 to Feb 2024 after approval from the ethical review board of Combined Military Hospital Rawalpindi (vide letter no. 430 and Clinical trial registration Id IRCT20230819059186N2). 110 (minimum sample size calculated 50) patients between ages 45-70 years were included in the study (55 in each of the two groups) after calculating the sample size using WHO calculator keeping the confidence interval at 95%, power of test at 90% (population variance 10000) with mean difference between first time to rescue analgesia of both groups being 65 ± 2 minutes after conducting a pilot study with 15 participants in both groups. The method of sampling was non-probability consecutive sampling by lottery method according to the inclusion criteria furnished.

Inclusion Criteria: ASA-II and III patients of COPD diagnosed by PFTs (pulmonary function test) with optimized disease between ages 45-70 years presenting in the general surgical department for elective cholecystectomy for cholelithiasis were included.

Exclusion Criteria: Patients with major cardiac or respiratory disease, low ejection fraction, unoptimized for hypertension or diabetes, patients with cholecystitis, patients allergic to Acetaminophen, MgSO₄ or nalbuphine and patients unwilling to be included in the study were excluded from the study.

The study method included all patients as per the inclusion criteria furnished. The patients were divided into Group-M (n=55) receiving MgSO₄ and Acetaminophen and Group-N (n=55) receiving Nalbuphine (Figure). Once the patients were divided into two groups, an informed written consent was taken. Standard monitoring including non-invasive blood pressure, heart rate, capnography and ECG was attached to participants in both groups. The drugs in

both groups were prepared by a consultant anesthetist unaware of the study protocol with burettes marked X and Y with 100 ml Normal Saline. The prepared drugs were then given to the resident anesthetist on duty in the operating room also unaware of the study protocol. The patients were blinded to which group they were placed in using randomization as already furnished in the methodology. Patients in Group-M received intravenous MgSO₄ at 50 mg/kg diluted in 100 ml of Normal Saline over 15 minutes with intravenous Acetaminophen 15 mg/kg over 15 minutes before induction of anesthesia. Patients in Group-N received Nalbuphine 0.15 mg/kg diluted in 100 ml Normal Saline over 15 minutes before induction.

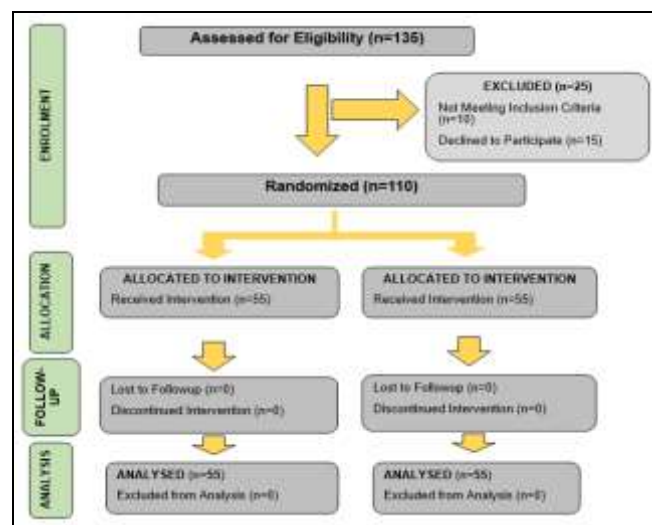


Figure: Phases of the Study

Anesthesia was induced in both groups with IV Propofol 2 mg/kg, IV Atracurium 0.5 mg/kg with maintenance done with 60% oxygen with Isoflurane at 1.0 MAC. Mean heart rate (HR) and mean arterial pressure (MAP) were observed between both groups per-operatively 15 minutes after surgical incision (HR 1 and MAP 1) and 15 minutes before extubation (HR 2 and MAP 2). Patients were extubated after Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/kg were given for reversal of the neuromuscular block.

Post-operatively, median pain scores were observed in both groups at 1, 3 and 6 hours. Time to first rescue analgesia was also noted with Group-M receiving infusion of MgSO₄ 10mg/kg and Intravenous Acetaminophen 7.5mg/kg while Group-N receiving Intravenous Nalbuphine 0.05mg/kg once the pain score on the visualanalog scale (VAS) was above 4.

Primary variables measured were per-operative mean heart rate, mean arterial pressure, time to rescue analgesia and median pain scores at 1-, 3- and 6-hour intervals. Secondary variables were the incidence of hypotension, respiratory depression, nausea and vomiting between both groups. Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. Independent samples t-test was used to compare statistical means between both groups. Median pain scores were compared using the Mann Whitney U test. A *p*-value of ≤ 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.00.

RESULTS

A total of 110 patients were included in the study divided into Group-M (n=55) and Group-N (n=55). Mean age of patients in Group-M was 66.07 ± 2.06 years versus 66.47 ± 2.02 years in Group-N ($p=0.307$). Mean weight was 67.82 ± 3.85 kg in Group-M versus 68.13 ± 3.89 kg in Group-N ($p=0.677$) (Table-I).

Table-I: Comparison of Age and Height Characteristics Between Both Groups (n=110)

Variable	Group-M (n=55)	Group-N (n=55)	<i>p</i> -value
Mean Age (Years)	66.07 ± 2.06	66.47 ± 2.02	0.307
Mean Weight (Kg)	67.82 ± 3.85	68.13 ± 3.89	0.677

Mean duration of surgery was 129.44 ± 7.21 minutes in Group-M versus 128.91 ± 6.46 minutes in Group-N ($p=0.687$). When observing the primary variables, mean time to first dose of rescue analgesia required was 122.49 ± 14.01 minutes in Group-M versus 151.71 ± 10.36 minutes in Group-N ($p<0.001$). When comparing the post-operative median pain scores, median pain score at 1 hour post-operatively was 3.00 (IQR=1.00) in Group-M versus 2.00 (IQR=1.00) in Group-N ($p=0.353$). Scores observed 3 hours post-operatively were 3.00 (IQR=0.00) versus 3.00 (IQR=0.00) between Group-M and Group-N ($p=0.626$). Finally, median pain scores 6 hours post-operatively showed 3.00 (IQR=0.00) versus 3.00 (IQR=0.00) between both groups respectively ($p=0.154$) (Table-II).

When the frequency of side effects was compared between both interventions, hypotension was observed in 10(18.2%) patients in Group-M versus 06(10.9%) patients in Group-N. Nausea was observed by 02(3.6%) participants in Group-M versus 12(21.8%) participants in Group-N. vomiting was seen in 01(1.8%) patients in Group-M versus 03(5.5%) patients in Group-N. Respiratory depression was seen in

01(1.8%) patient in Group-M versus 07(12.7%) patients in Group-N (Table-III).

Table-II: Comparison of Operative Parameters among Groups (n=110)

Variable(s)	Group-M (n=55)	Group-N (n=55)	<i>p</i> -value
Duration Of Surgery (Minutes)	129.44 ± 7.21	128.91 ± 6.46	0.687
Mean Time to First Dose Rescue Analgesia (Minutes)	122.49 ± 14.01	151.71 ± 10.36	<0.001
Median Post-Operative Pain Scores			
1 Hour Post Surgery	3.00 (IQR=1.00)	2.00 (IQR=1.00)	0.353
3 Hours Post Surgery	3.00 (IQR=0.00)	3.00 (IQR=0.00)	0.626
6 Hours Post Surgery	3.00 (IQR=0.00)	3.00 (IQR=0.00)	0.154

Table-III: Comparison of Incidence of Side Effects Between Both Groups (n=110)

Variable(s)	Group-M (n=55)	Group-N (n=55)
Hypotension	10(18.2%)	06(10.9%)
Nausea	02(3.6%)	12(21.8%)
Vomiting	01(1.8%)	03(5.5%)
Respiratory Depression	01(1.8%)	07(12.7%)

DISCUSSION

The findings of our study show that intravenous Magnesium Sulphate with Acetaminophen is a good alternative to Nalbuphine and provides statistically significant superior adverse effect profile than Nalbuphine in patients with COPD.

This study was carried out at our center with the aim of comparing non-opioid based options for pain relief in patients where the chances of complications are more when using opioids. Patients with chronic obstructive pulmonary disease are already compromised with respect to respiratory reserve, lung compliance and the effect of volatile anesthetics hamper the physiological compensatory responses affecting the ventilation perfusion ratio. We used the non-opioid analgesia options available at our center and studied whether they can provide effective analgesia providing an excellent alternative that may result in better post-operative recovery and early discharge.

Among the primary variables studied, the non-opioid combination of intravenous Magnesium Sulphate and Acetaminophen was able to provide statistically and clinically comparable results when the median pain scores were observed at the specified post-operative intervals. Similar studies were carried out by H Soleimanpour *et al.*,⁹ and MB El Mourad *et al.*,¹⁰ who concluded that intravenous Magnesium Sulphate proved to be a good analgesic alternative as compared with conventional analgesics. Not only did it provide adequate analgesia in minor and low risk surgeries but was also beneficial in providing good

peri-operative hemodynamic parameters. The excellent hemodynamic stability was also seen during studies done by W Tan *et al.*,¹¹ and J Greenwood *et al.*,¹². The corroborative studies along with results from ours make it a very attractive candidate for analgesia and hemodynamic stability. The reason we added intravenous Acetaminophen was to provide an added level of analgesia when compared to the superior efficacy of opioids. Studies done Modir *et al.*, showed that as compared with single use of intravenous Magnesium, adjuvant therapy improved the overall pain scores and patients satisfaction without adversely hampering the hemodynamic profile.¹³ However, when comparing the mean time to first dose of rescue analgesia, it was observed that intravenous Nalbuphine was associated with a longer time required. Even though the mean time between the two was statistically significant, it was not clinically profound when seen in our patient group. The use of magnesium per-operatively has also been proposed to improve lung mechanics and oxygenation especially in compromised individuals like ARDS, pneumonia and COPD.¹⁴

Local studies done on Magnesium Sulphate as an analgesic within our demographic area after orthognathic surgeries were also consistent with good pain toleration, decreased overall pain scores and provided better patient satisfaction.¹⁵ The hemodynamic stability profile was also consistent with similar studies when Magnesium was used in cardiac surgery.¹⁶

A profound and superior effect was seen when observing patients post-operatively in our study. The adverse effect profile of Magnesium Sulphate was more conducive than Nalbuphine when patients were kept in the HDU prior to discharge and were given these agents for pain relief.¹⁷ There was no incidence of respiratory depression in the Magnesium Sulphate group whereas it was a problem seen in a good number of patients in the alternate group. The frequency of vomiting was also increased in the opioid group.¹⁸ This provides an attractive alternative in COPD patients where multiple co-morbid are already a concern for close monitoring.

RECOMMENDATIONS

The study recommends the use of intravenous Magnesium Sulphate with Acetaminophen in providing good analgesia in patients of COPD.

LIMITATION OF STUDY

The limitations are that the study is a single center study. We only compared Nalbuphine, other opioids need to

be compared to see analgesic comparability. We added Acetaminophen with the Magnesium Sulphate regimen to augment the analgesia provided since the strength is not on par with opioids according to literature. More studies are needed to see whether Magnesium Sulphate can be used as a sole agent or not.

CONCLUSION

We conclude that intravenous Magnesium Sulphate with Acetaminophen is a good alternative and provides superior adverse effect profile than Nalbuphine in patients with COPD.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SAAS & MRI: Data acquisition, data analysis, critical review, approval of the final version to be published.

RASK & TM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AS & HT: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

- Rodrigues SdO, Cunha CMCd, Soares GMV, Silva PL, Silva AR, Gonçalves-de-Albuquerque CF. Mechanisms, pathophysiology and currently proposed treatments of chronic obstructive pulmonary disease. *Pharmaceuticals* 2021; 14(10): 979. <https://doi.org/10.3390/ph14100979>
- Meiwald A, Gara-Adams R, Ma Y, Bhutani M, Ichinose M, Scullion J, et al. Analysing the COPD care pathway in Japan, Canada, England and Germany: a global view. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 1507-1521. <https://doi.org/10.2147/copd.s360983>
- Bostock B. Capturing the missing millions with COPD. *Pract Nurs* 2022; 33(Sup11): S3-S5. <https://doi.org/10.12968/pnur.2022.33.Sup11.S3>
- Ayilya BL, Nazeer RA. Epidemiological burden, risk factors, and recent therapeutic advances in chronic obstructive pulmonary disease. *J Adv Biotechnol Exp Ther* 2023; 6: 109. <https://doi.org/10.5455/jabet.2023.d110>
- Liao K-M, Tseng C-J, Chen Y-C, Wang J-J, Ho C-H. Outcomes of laparoscopic cholecystectomy in patients with and without COPD. *Int J Chron Obstruct Pulmon Dis* 2019; 1159-1165. <https://doi.org/10.2147/COPD.S201866>
- Baillargeon J, Singh G, Kuo Y-F, Raji MA, Westra J, Sharma G. Association of opioid and benzodiazepine use with adverse respiratory events in older adults with chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2019; 16(10): 1245-1251. <https://doi.org/10.1513/AnnalsATS.201901-024OC>
- Corsi AJ, Ali AS, Kumar D. Self-Inflicted Abdominal Air Insufflation Leading to Diffuse Subcutaneous Emphysema, Pneumoperitoneum, Pneumomediastinum, Pneumopericardium, and Pneumothorax: A Case Report. *Cureus* 2022; 14(10): e302728. <https://doi.org/10.7759/cureus.30278>

8. Fiore JF, El-Kefraoui C, Chay M-A, Nguyen-Powanda P, Do U, Olleik G, et al. Opioid versus opioid-free analgesia after surgical discharge: a systematic review and meta-analysis of randomised trials. *Lancet* 2022; 399(10343): 2280-2293.
[https://doi.org/10.1016/S0140-6736\(22\)00582-7](https://doi.org/10.1016/S0140-6736(22)00582-7)
9. Soleimanpour H, Imani F, Dolati S, Soleimanpour M, Shahsavarinia K. Management of pain using Magnesium Sulphate : A narrative review. *Postgrad Med* 2022; 134(3): 260-266. <https://doi.org/10.1080/00325481.2022.2035092>
10. El Mourad MB, Arafa SK. Effect of intravenous versus intraperitoneal magnesium sulfate on hemodynamic parameters and postoperative analgesia during laparoscopic sleeve gastrectomy-A prospective randomized study. *J Anaesthesiol Clin Pharmacol* 2019; 35(2): 242.
https://doi.org/10.4103/joacp.joacp_208_18
11. Tan W, Qian D-c, Zheng M-m, Lu X, Han Y, Qi D-y. Effects of different doses of magnesium sulfate on pneumoperitoneum-related hemodynamic changes in patients undergoing gastrointestinal laparoscopy: a randomized, double-blind, controlled trial. *BMC Anesthesiol* 2019; 19: 1-11.
<https://doi.org/10.1186/s12871-019-0886-4>
12. Greenwood J, Nygard B, Brickey D. Effectiveness of intravenous magnesium sulfate to attenuate hemodynamic changes in laparoscopic surgery: A systematic review and meta-analysis. *JBIS Evid Synth* 2021; 19(3): 578-603.
<https://doi.org/10.11124/jbisr-d-19-00414>
13. Modir H, Moshiri E, Khamene MP, Komijani D. Comparison of adjuvant therapy with midazolam, paracetamol, tramadol, or magnesium sulfate during intravenous regional anesthesia with ropivacaine: A randomized clinical trial. *Int J Crit Illn Inj Sci* 2023; 13(1): 11.
https://doi.org/10.4103/ijciis.ijciis_39_22
14. Ahmed A, Sayed AH, Elkholy J, Elshal S, Badwy A, Abdelhamid B, et al. Intraoperative MgSO₄ infusion protects oxygenation and lung mechanics in COPD patients during general anesthesia. A randomized clinical trial. *Acta Anaesthesiol Scandinavica* 2020; 64(10): 1460-1468.
<https://doi.org/10.1111/aas.13684>
15. Qureshi R, Kaleem HM, Toosy WJ, Imtiaz M, Farooq M. A Clinical Trial of Patient Reported Alterations in Pain and Opioid Intake Following Paracetamol and Magnesium Sulfate after Orthognathic Surgery. *Paki J Med Health Sci* 2023; 17(03): 425-428. <https://doi.org/10.53350/pjmhs2023173425>
16. Khalid V, Khuwaja MA, Ahmed A, Kumar K, Iqtdar R, Hussain SA. Magnesium Sulphate Versus Lignocaine At Induction For Hemodynamic Response In Patients Undergoing Cardiac Surgery. *Pak Armed Forces Med J* 2021; 71(Suppl-2): S338-S342.
17. Zhibin W, Yingwei D. Observation of magnesium sulfate in improving anesthesia effect in children undergoing laparoscopic surgery. *J New Med* 2020; 51(6): 450.
<https://doi.org/10.3969/j.issn.0253-9802.2020.06.009>
18. Noland A. Intravenous Magnesium Sulfate for Multimodal Analgesia. *Anesth J* 2019; 7: 17-18.
<https://doi.org/10.18776/qrsf6088>